March 2, 2000

MEMORANDUM

SUBJECT: Response to Public Comments on the Preliminary Risk Assessment(s) for the Organophosphate Pirimiphos-methyl

FROM: Lorilyn M. McKay, Chemical Review Manager
Special Review and Reregistration Division
Office of Pesticide Programs

TO: OPP Public Docket for Pirimiphos-methyl
Docket #34168

The attached document addresses public comments that were received in response to EPA's Notice of Availability (64 FR No.5, 1199-1200; January 9, 1999) of the preliminary risk assessment for the organophosphate chemical pirimiphos-methyl. Seven comments were received during the open public comment period.

Since the close of the public docket in March 1999, refinements have been made to the Human Health risk assessments for pirimiphos-methyl - endpoints have been revised and the risk assessments have been refined significantly. The HED Hazard Identification Assessment Review Committee (HIARC) subsequently reevaluated the human studies for the purpose of risk assessment, and concluded that the human studies were inadequate for risk assessment purposes. The HIARC then selected doses and endpoints from the appropriate animal toxicity studies. For further information on how these studies and refinements impacted the risk assessments, please refer to the revised human health risk assessment now available in the Public Docket and on the Agency's website: **www.epa.gov/pesticides.**

The comments are summarized below, followed by the Agency's response.

All of the comments received for the EPA preliminary risk assessment were submitted by Schering-Plough Animal Health, the registrant responsible for all animal end-use products for pirimiphos-methyl. All comments received from Schering-Plough Animal Health are in pursuit of a pirimiphos-methyl cattle pour-on product for registration. Their comments related only to the human health risk assessment.

1. Comments Related to Requirement of Dermal Nature and Dermal Magnitude Studies

Comment: Schering-Plough Animal Health objects to the requirement for a dermal nature of residue study, for registration of the proposed cattle pour-on product. Further, Schering-Plough Animal Health contends that an ear tag and direct dermal application should not be incorporated into the same magnitude of residue study.

Response: EPA maintains that dermal nature and dermal magnitude of residue studies would be necessary if the registrant intends to submit an application for registration of a pour-on product for cattle. EPA has specific guidelines that are followed to ensure compliance with registration requirements. Additional animal metabolism studies, (i.e. a nature of residue study), can be required if direct dermal or inhalation application to livestock is proposed. These additional studies are necessary to determine whether dermal or inhalation exposure results in the same metabolic pattern as oral dosing.

In following current guideline procedures, EPA believes that it is necessary to require both the ear tag and direct dermal applications as part of the same magnitude of residue study since it is expected that if a pour-on product were applied directly onto cattle, the product would lead to more residues, therefore making a dermal nature study necessary. In addition, because current labels **do not** prohibit ear tag and dermal application of pirimiphos-methyl, simultaneously, it seems possible that the scenario might occur. Therefore, EPA maintains the requirement of an ear tag use and direct dermal application use in the same magnitude of residue study in order to completely assess residue detection.

All new registration applications for pirimiphos-methyl will have to conform to the new RED requirements set forth after the organophosphate process (OP Process) has been completed. All new registration applications are to be handled by the Registration Division and will have to comply with all new EPA requirements for the organophosphate set forth by the Special Review and Reregistration Division. At this time, EPA maintains that the reregistration process for pirimiphos-methyl, and a cumulative risk assessment for all OP's, must be completed before the acceptance of new registrations can occur for this organophosphate.

2. Comment Related to Dietary and Worker Exposure Assessment

Comment: Schering-Plough contends that the EPA preliminary dietary exposure and worker exposure assessment were inconsistent. Schering-Plough noted that the dietary exposure estimate **did not** include their pending pour-on use (did however include Wilbur-Ellis pending grain storage bin use), but the ORE worker assessment did.

Response: The Agency notes that the pour-on use was incorporated into the ORE assessment dated June 1, 1999, but is not included in the comprehensive risk assessment dated July 13, 1999 since it is not a registered use. No consideration will be given to the worker risk associated with the cattle pour-on use during the reregistration process.

3. Comment Related to Meat and Meat By-Product Tolerances

Comment: Schering-Plough objects to EPA's recommendation to lower or revoke animal meat, fat, and meat by-products. Schering-Plough contends that the tolerances should be maintained at 0.2 ppm for fat, meat and meat by-products.

Response: EPA believes that based on currently registered uses and available residue data, a reduction in tolerances in residues for animal commodities is appropriate for this organophosphate. All of EPA's tolerance reassessment decisions are based on current uses and science. Before any new uses are allowed, such as the proposed pour-on cattle use, all existing uses must meet the FQPA standard and be determined to be safe before a new use is registered. EPA can make decisions to lower or revoke tolerances completely, an outcome that assures safety for all consumers, particularly infants and children.

4. Comment Related to Toxicology Data Gaps and the Additional Uncertainty Factors

Comment: Schering-Plough contends that toxicological datagaps cited in the preliminary risk assessment were incorrect. An acute delayed neurotoxicity study in hens, a chronic dog study, and a combined chronic/carcinogenicity rat study were submitted in March 1998. They object to the Agency's use of an additional 10X uncertainty factor that was added because of use of LOAELS, rather than NOAELS, in determining toxicity endpoints. Schering-Plough contends that the 3X uncertainty studies should be removed given that all toxicological studies have not been considered.

Response: According to the Agency's records, the three studies cited as datagaps were received by the Agency in December 1997. The chronic studies were found to be deficient. The chronic toxicity study in dogs and combined chronic toxicity/carcinogenicity study in rats remains outstanding. A 3000 fold safety factor to be deemed appropriate given that no NOAELs were achieved in the studies considered in selecting toxicity endpoints. The neurotoxicity study(ies) in hens did not meet guideline requirements, but did provide a reasonable understanding for pirimiphos-methyl with respect to delayed neurotoxicity in hens. The sparse data submitted to the Agency indicate that there is no increased sensitivity among fetuses or pups following pre and/or post-natal exposure. Therefore, the FQPA safety factors has been reduced from 10X to 3X. The

available data however are not adequate to evaluate neurotoxicity following acute and long term exposure, or to assess the functional development of young animals and in turn the susceptibility to infants and children. It should be noted that the Agency recently issued a Data Call-In (DCI) for developmental neurotoxicity studies for all organophosphates, including pirimiphos-methyl.

5. Comment Related To Endpoint Selection Process

Comment: Schering-Plough contends that the toxicological endpoint selection process should be revisited, and that the dietary exposure assessment should be revised to include tolerance levels (i.e. animal tolerances), not anticipated residues.

Response: Since the preliminary risk assessment, the Agency has concluded that the human studies were not appropriate for risk assessment purposes. The Agency selected doses and endpoints from available animal toxicity studies, and revised the acute and chronic dietary exposure and risk analyses.

The use of anticipated residues for the revised risk assessment results in dietary risks below the Agency's level of concern in the most refined analyses. The revised anticipated residues actually result in significant reduction of the dietary exposure and risk estimates relative to the reassessed tolerances and previous analyses. The Agency has assessed the entire toxicology database for pirimiphos-methyl as recently as May 1999. All available data, including the three cited by Schering-Plough, have been considered.